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ORIGINAL ARTICLE

Effect of Dragon Fruit *Dadih* Fortified With Selenium on SREBP-1C Expression and Liver Histopathology in Obese Rats

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Abstract

Background/Aim: Obesity remains a major global health challenge, closely linked to an increased likelihood of developing metabolic disorders, such as non-alcoholic fatty liver disease (NAFLD), insulin resistance, type 2 diabetes and cardiovascular complications. This study aimed to investigate the effect of selenium-fortified dragon fruit *dadih* on sterol regulatory element-binding protein-1c (SREBP-1c) expression and liver histopathology in obese rats induced by a high-fat, high-fructose diet (HFFD).

Methods: *Dadih*, a traditional Indonesian fermented dairy product, was enriched with selenium (0.4 ppm) and 10 % red dragon fruit juice to enhance its antioxidant and metabolic regulatory properties. Thirty-six male Sprague-Dawley rats were divided into four groups: healthy control (K–), obesity control (K+), *dadih* (Di) and selenium-fortified dragon fruit *dadih* (Di+). After 28 days of intervention, liver tissues were analysed for SREBP-1c expression and histopathological alterations.

Results: The results showed a significant increase in hepatic SREBP-1c expression in the obese control group (2172.8 ± 32.3 pg/mL) compared to the healthy control (999.2 ± 45.5 pg/mL; $p < 0.001$). Intervention with Di reduced SREBP-1c expression to 1455.2 ± 40.3 pg/mL. At the same time, the Di+ group showed a greater reduction to 1174.0 ± 58.8 pg/mL ($p < 0.001$), suggesting a more potent suppression of hepatic lipogenesis with selenium and dragon fruit enrichment. Histopathological analysis revealed hepatocyte ballooning and inflammatory cell infiltration in the obese control group, indicating early signs of liver injury. Although steatosis was not yet prominent due to the relatively short 28-day induction period, structural alterations in hepatocytes were already evident and likely associated with elevated SREBP-1c expression. These pathological changes were attenuated in the intervention groups, especially in Di+, which showed more pronounced improvements in liver architecture.

Conclusion: Selenium-fortified dragon fruit *dadih* holds promise as a functional dietary intervention to attenuate hepatic lipogenesis and protect against obesity-induced liver damage by downregulating SREBP-1c. Further studies are warranted to evaluate its long-term effects and underlying molecular mechanisms.

Key words: Obesity; Selenium-fortified *dadih*; Sterol regulatory element binding protein 1; Dairy products; Non-alcoholic fatty liver disease; Metabolism; Health.

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Introduction

Obesity remains a major global health challenge, with its prevalence continuing to rise across the world. As reported by the World Health Organisation (WHO), obesity rates have nearly tripled since 1975, affecting individuals across different age groups and socioeconomic backgrounds. This condition is closely linked to an increased likelihood of developing metabolic disorders, such as non-alcoholic fatty liver disease (NAFLD), insulin resistance, type 2 diabetes and cardiovascular complications. A significant factor driving lipid accumulation in the liver is the activation of sterol regulatory element-binding protein-1c (SREBP-1c). This transcription factor plays a crucial role in lipogenesis by enhancing fatty acid synthesis while suppressing fatty acid oxidation.[1] The upregulation of SREBP-1c has been extensively linked to hepatic steatosis and the progression of NAFLD, making it a crucial target in obesity-related metabolic dysfunction.

Functional foods, particularly fermented dairy products, have been proposed as potential dietary interventions to regulate lipid metabolism and improve metabolic health. *Dadih* is a traditional fermented dairy product made from buffalo milk in West Sumatra, Indonesia, naturally fermented through spontaneous fermentation without the use of a starter culture.[2] The fermentation process occurs anaerobically at room temperature (28–30 °C) for 24–48 hours within bamboo tubes, allowing the natural growth of lactic acid bacteria (LAB), which play a role in modulating the gut microbiota, reducing cholesterol and enhancing the immune system.[3]

Despite its potential health benefits, previous studies have reported that *dadih* has a relatively low antioxidant activity (IC50: 1177.637 ppm).[4] To enhance the functional properties of *dadih*, the incorporation of red dragon fruit *(Hylocereus polyrhizus)* has been explored. This tropical fruit is rich in betalains, flavonoids, phenolic compounds and vitamin C, which contribute to antioxidant and anti-inflammatory effects.[5] A previous study demonstrated that *dadih* with 10 % red dragon fruit extract was preferred over regular *dadih*, exhibiting a higher total lactic acid bacteria (LAB) count and antioxidant capacity.[4]

In addition to dragon fruit, selenium (Se) fortification is another promising strategy to enhance the health benefits of *dadih*. Selenium is a vital trace element known for its potent antioxidant and anti-inflammatory effects. It is a key component of glutathione peroxidase (GPx), an enzyme that safeguards cells against oxidative damage and contributes to the regulation of lipid metabolism.[6] Selenium has also been found to interact with sirtuin 1 (SIRT1), inhibiting SREBP-1c activity and thereby reducing hepatic lipid accumulation, which prevents fatty liver disease. Previous research has demonstrated that selenium-enriched probiotics significantly reduce serum triglyceride and cholesterol levels, improve liver histopathology and downregulate the expression of lipogenic genes.[6]

The combined effect of selenium-fortified red dragon fruit *dadih* on SREBP-1c expression and liver histopathology has not been previously investigated. This study aimed to evaluate whether this innovative functional food can serve as a dietary intervention to modulate lipid metabolism, specifically by regulating SREBP-1c, reduce hepatic fat accumulation and improve metabolic health in obese rats. Since SREBP-1c is a key regulator of lipogenesis, its modulation is a key focus in assessing the potential protective effects of this intervention on liver histopathology.

Methods

This experimental study employed a completely randomised post-test-only control group design. A total of 24 male Sprague-Dawley rats (8 weeks old, weighing 150–200 g) underwent a 7-day acclimation phase before being randomly divided into four groups, each consisting of six rats. The healthy control group (K-) was provided with standard feed and water *ad libitum*, whereas the obesity control group (K+) was subjected to a high-fat, high-fructose diet (HFFD) for 28 days to induce obesity. The *dadih* group (Di) consisted of obese rats receiving 2 mL/200 g BW/day of *dadih*. In comparison, the selenium-fortified *dadih* group (Di+) consisted of obese rats receiving 2 mL/200 g BW/day of selenium-fortified dragon fruit *dadih*. *Dadih* was prepared traditionally by heating 1000 mL of buffalo milk to 72 °C for 15 seconds, followed by cooling to 30 °C. For the fortified formulation, 10 % red dragon fruit juice and 0.4 ppm of selenium (Na_2SeO_3) were added to the milk. Previ-

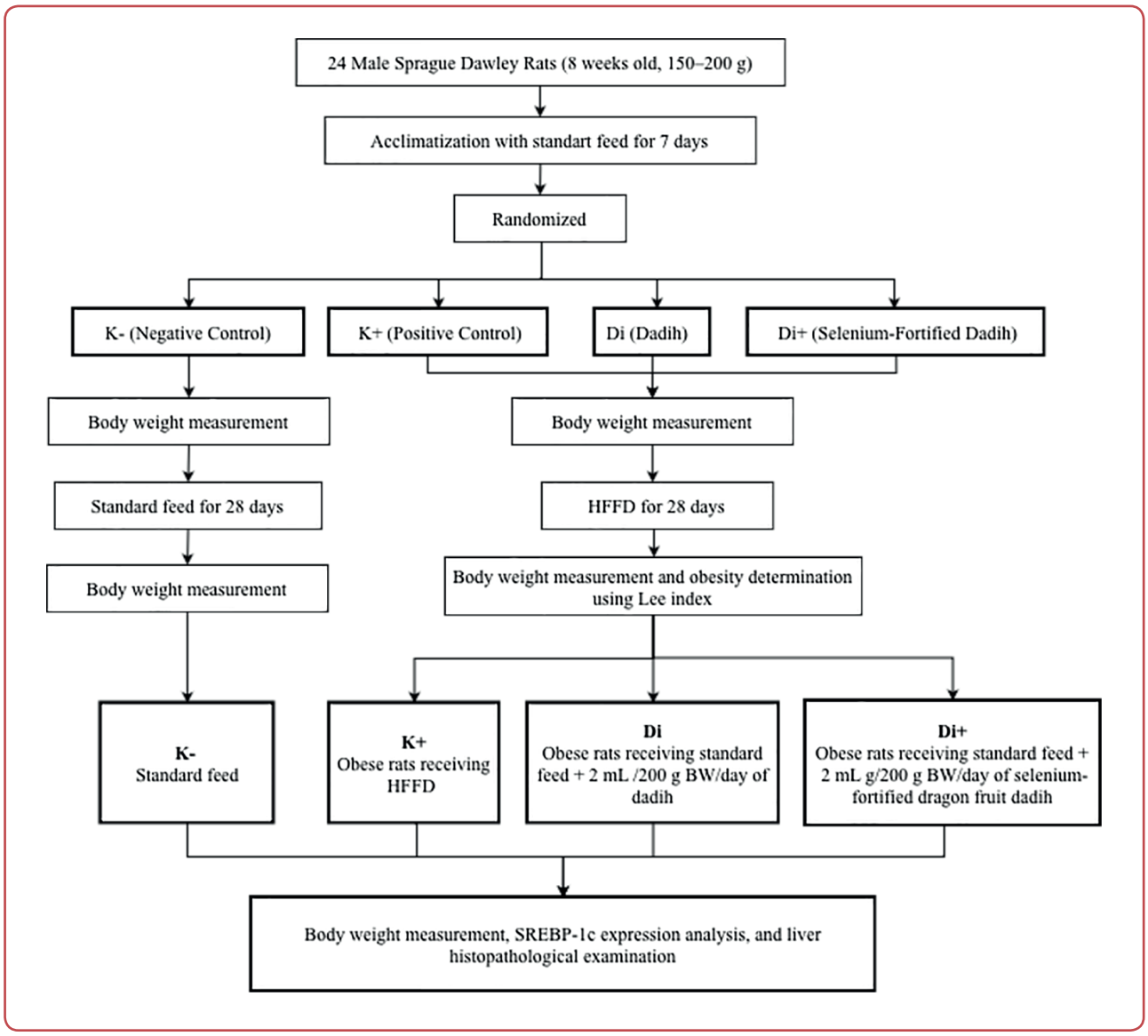

Figure 1: Experimental design of study

HFFD: high-fat, high-fructose diet; SREBP-1c: sterol regulatory element-binding protein-1c;

ous studies have shown that selenium supplementation at a concentration of 0.4 ppm is optimal, yielding favourable organoleptic results in terms of the chemical, microbiological, rheological and sensory properties of fermented milk.[7] After 28 days of intervention, all rats were euthanised and liver tissue samples were collected for further analysis. The experimental design of this study is presented in Figure 1.

Obesity was induced using a HFFD for 28 days, consisting of 3 g pork fat (15 %), 2 g duck egg yolk (10 %), 15 g standard chow (75 %) and an additional 2 mL of 1 % fructose solution. Body weight was monitored weekly and obesity was confirmed using Lee's index (a value greater than 300). Rats exceeding this threshold were included in the intervention phase. Liver tissue samples were homogenised and centrifuged at 10,000 × g for 10 minutes at 4 °C, then analysed using an ELISA kit (*EKL Biotechnology*, USA). Absorbance was recorded at 450 nm and SREBP-1c concentration was quantified based on a standard curve. Liver tissue samples were preserved in 10 % formalin, embedded in paraffin, sectioned to a thickness of 5 µm and stained using haematoxylin and eosin (H&E). The histopathological assessment focused on steatosis, inflammation and hepatocyte ballooning.

All statistical analyses were conducted using SPSS 26 for Windows (IBM Analytics, Armonk, NY, USA). Data were expressed as mean ± standard deviation (SD). The Shapiro-Wilk test was used to assess the normality of the data distribution. For normally distributed data, a one-way

ANOVA was performed, followed by the Bonferroni post hoc test. In contrast, for non-normally distributed data, the Kruskal-Wallis test was used, followed by the Mann-Whitney U test. A p-value of less than 0.05 was considered statistically significant.

Results

Body weight

Body weight changes were observed in all rat groups throughout the intervention period in this study (Figure 2A). The healthy control group (K-) exhibited a lower weight gain compared to the disease control group (K+), while the groups receiving *dadih* intervention (Di) and selenium-fortified dragon fruit *dadih* (Di+) showed a more controlled weight gain pattern.

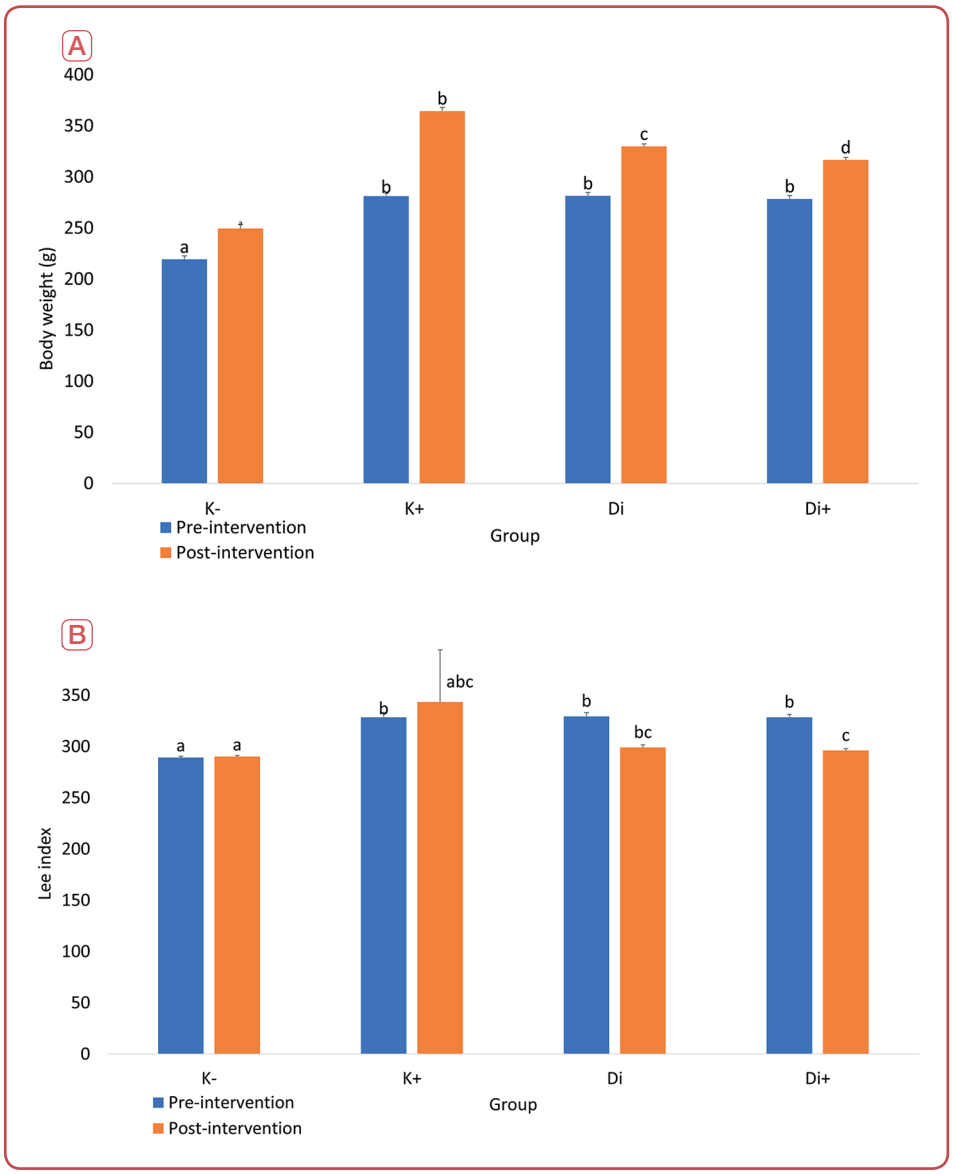

Figure 2: *Changes in body weight (A) and Lee index (B) during the intervention*

Body weight data are expressed as mean ± SD, whereas Lee index data are presented as median (N = 6). Statistical analysis for body weight was conducted using one-way ANOVA, followed by the Bonferroni post hoc test. In contrast, the Lee index was analysed using the Wilcoxon test, followed by the Mann-Whitney post hoc test. A p-value of less than 0.05 was considered statistically significant. Different superscript letters (a, b, c, d) denote significant differences between groups. The healthy control group (K-) was provided with standard feed and water ad libitum. The obesity control group (K+) was subjected to a high-fat, high-fructose diet (HFFD) for 28 days to induce obesity. The dadih group (Di) consisted of obese rats receiving 2 mL/200 g BW/day of dadih. The selenium-fortified dadih group (Di+) consisted of obese rats receiving 2 mL/200 g BW/day of selenium-fortified dragon fruit dadih.

Based on the statistical analysis, a significant difference in body weight was observed across all groups after the intervention, with a p-value of 0.000. The paired t-test results indicated a substantial change in body weight within each group before and after the intervention, while the one-way ANOVA. The Bonferroni post hoc test further confirmed significant differences between the groups. Figure 2B illustrates the changes in Lee index across all groups during the intervention. The groups receiving HFFD had a Lee index greater than 300, confirming the successful induction of obesity, making them suitable for further research on dietary interventions and metabolism. The healthy control group (K-) exhibited a lower weight gain compared to the disease control group (K+), while the groups receiving *dadih* intervention (Di) and *dadih* supplemented with dragon fruit and selenium (Di+) demonstrated a more controlled weight gain pattern.

SREBP-1c expression

The analysis of SREBP-1c expression, as presented in Table 1, indicates that HFFD administration significantly increased SREBP-1c expression compared to the healthy control group (K-) ($p = 0.000$). The K+ group exhibited the highest SREBP-1c expression level (2172.8 ± 32.3 pg/mL), while the K- group had the lowest expression (999.2 ± 45.5 pg/mL). This finding suggests that a high-fat, high-fructose diet induces SREBP-1c activation, a crucial factor in enhancing hepatic lipid synthesis.

The healthy control group (K-) was provided with standard feed, whereas the obesity control group (K+) was administered an high-fat, high-fructose diet (HFFD) for 28 days. The *dadih* group (Di) consisted of obese rats receiving standard feed + 2 mL/200 g body weight/day of *dadih*. In comparison, the selenium-fortified *dadih* group (Di+) consisted of obese rats receiving standard feed plus 2 mL/200 g body weight/day of selenium-fortified dragon fruit *dadih*. Data are expressed as mean ± SD (N = 6). Statistical analysis was conducted using one-way ANOVA followed by the Bonferroni post hoc test, with statistical significance set at $p < 0.05$.

Intervention with *dadih* (Di) and selenium-fortified *dadih* (Di+) significantly suppressed SREBP-1c expression compared to the K+ group ($p = 0.000$). The Di group showed a reduction in SREBP-1c expression (1455.2 ± 40.3 pg/mL), while the Di+ group exhibited a greater decrease (1174.0 ± 58.8 pg/mL). This difference suggests that selenium fortification in *dadih* provides an additional effect in suppressing HFFD-induced SREBP-1c activation.

Table 1: Differences in SREBP-1c expression among treatment groups after intervention

Group	SREBP-1c expression (Mean ± SD)	p^1			
		K-	K+	Di	Di+
K-	999.2 ± 45.5	-	0.000*	0.000*	0.000*
K+	2172.8 ± 32.3	-	-	0.000*	0.000*
Di	1455.2 ± 40.3	-	-	-	0.000*
Di+	1174.0 ± 58.8	-	-	-	-
p	0.000				

(*) indicate significant differences ($p < 0.05$); SREBP-1c: sterol regulatory element-binding protein-1c;
The healthy control group (K-) was provided with standard feed and water ad libitum. The obesity control group (K+) was subjected to a high-fat, high-fructose diet (HFFD) for 28 days to induce obesity. The dadih group (Di) consisted of obese rats receiving 2 mL/200 g BW/day of dadih. The selenium-fortified dadih group (Di+) consisted of obese rats receiving 2 mL/200 g BW/day of selenium-fortified dragon fruit dadih.

Liver histopathology

The histopathological examination results are presented in Figure 3, which illustrates the macroscopic appearance of the liver, while Figure 4 depicts the microscopic liver histology across different treatment groups. Additionally, the quantitative assessment of liver damage, including inflammation, hepatocyte ballooning and steatosis, is summarised in Table 2, based on the NAFLD activity score (NAS). These findings provide a comprehensive evaluation of the structural alterations induced by HFFD and the potential protective effects of *dadih* and selenium-fortified *dadih* in mitigating liver damage associated with obesity-induced metabolic dysfunction.

The histopathological findings indicate that the healthy control group (K-) exhibited standard liver structure without signs of inflammation, ballooning, or steatosis. In contrast, the obesity control group (K+), which received a HFFD for 28 days, showed increased inflammation with a median score of 1 (range 1–2), along with significantly higher levels of hepatocyte ballooning and steatosis compared to the other groups ($p < 0.05$). The *dadih* intervention group (Di) demonstrated improvements, with lower inflammation and ballooning scores compared to K+, although some morphological alterations persisted. Meanwhile, the selenium-fortified *dadih* group (Di+) exhibited further enhancements, with lower

inflammation, ballooning and steatosis scores compared to K+ and approaching those of K-. Statistical analysis revealed significant differences between the K+ and intervention groups ($p < 0.05$), indicating the protective effects of the *dadih* intervention against liver damage induced by a high-fat, high-fructose diet. The quantitative assessment of liver damage, including inflammation, hepatocyte ballooning and steatosis, is presented in Table 2. Statistical analysis using the Kruskal-Wallis test revealed significant differences in inflammation, ballooning and steatosis among the groups ($p < 0.000$). Post hoc analysis using the Mann-Whitney test showed that

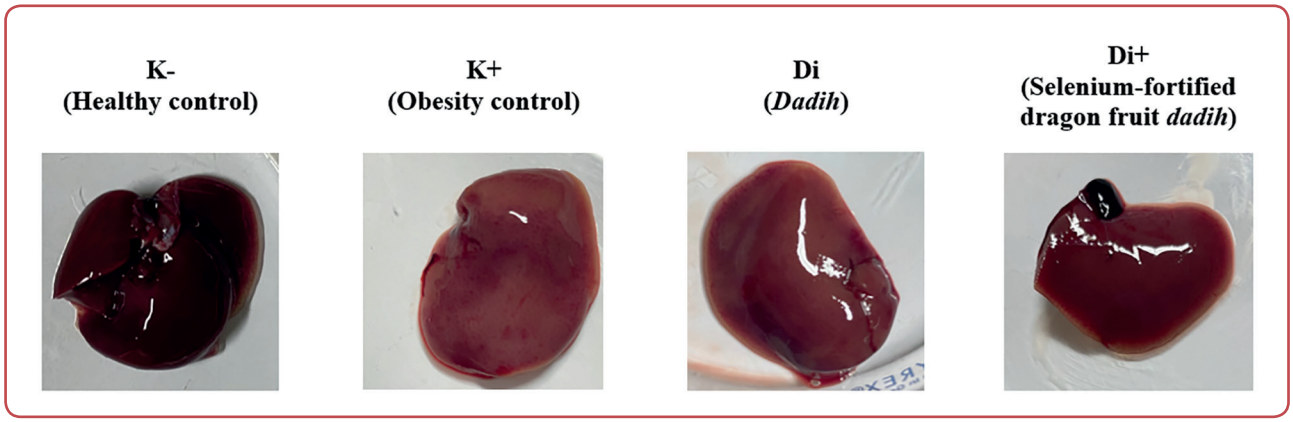

Figure 3: *Macroscopic appearance of rat liver across different treatment groups*

The liver in the healthy control group (K-) appeared normal, with a dark red, homogenous colour and a smooth surface. In contrast, the high-fat, high-fructose diet (HFFD)-induced group (K+) exhibited a paler colouration, indicating possible inflammation or lipid accumulation. The dadih intervention group (Di) showed partial improvement, with a colour closer to normal, though some changes remained. Meanwhile, the group receiving selenium- and dragon fruit-fortified dadih (Di+) had the most normal-looking liver appearance.

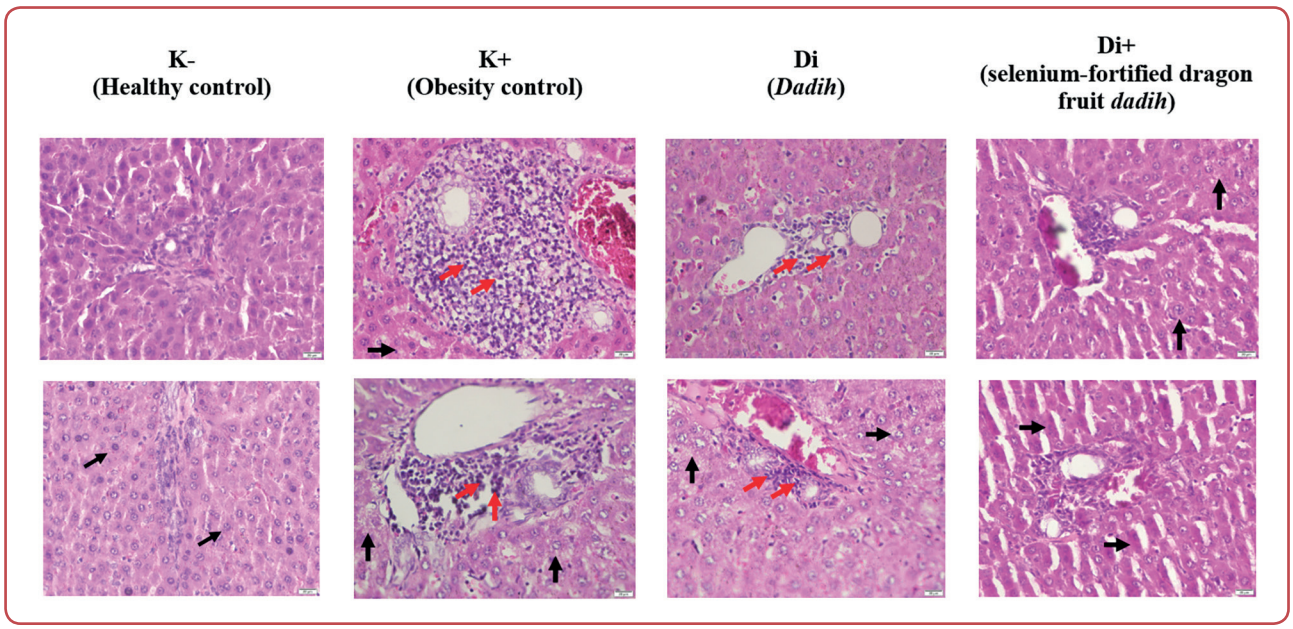

Figure 4: *Histopathological features of rat liver in different treatment groups (HE staining, 400x)*

The red arrow indicates hepatocyte ballooning and the black arrow indicates inflammatory cell infiltration. The image was taken using a light microscope at 400 x magnification with haematoxylin-eosin (H&E) staining. Histopathological analysis revealed significant structural differences in hepatocytes among the treatment groups. The K-group exhibited normal liver morphology, characterised by polygonal hepatocytes, centrally located nuclei and homogeneous eosinophilic cytoplasm, without intracellular granules or signs of inflammation. No inflammatory cells were observed, indicating a healthy liver condition. In contrast, the K+ group, induced with high-fat, high-fructose diet (HFFD), showed hepatocyte ballooning, intracellular accumulation and oedematous cytoplasm. Mononuclear inflammatory cells, primarily lymphocytes and plasma cells, were present around the portal area, characterised by moderate inflammation, indicating metabolic stress and early-stage liver damage. The dadih intervention group (Di) demonstrated structural improvement compared to K+, with reduced hepatocyte ballooning and lower inflammatory cell infiltration. However, some hepatocyte alterations persisted, suggesting partial recovery. The Di+ group showed better results than Di, with fewer ballooned hepatocytes and the absence of periportal inflammatory cells, indicating greater reduction in inflammation. Some areas exhibited hepatocyte structures approaching normal conditions, suggesting that selenium and dragon fruit fortification provided more substantial protective effects against oxidative stress and inflammation.

Table 2: Inflammation, ballooning and steatosis scores based on NAFLD activity score (NAS)

Group	Inflammation median (min-max)	p¹			
		K-	K+	Di	Di+
K(-)	0 (0 – 0)	-	0.000*	0.189	0.005*
K(+)	1 (1 – 2)	-	-	0.000*	0.000*
Di	0 (0 – 1)	-	-	-	0.929
Di+	0 (0 – 1)	-	-	-	-
p	0.000				
Group	**Ballooning median (min-max)**	**p¹**			
		K-	K+	Di	Di+
K(-)	0 (0 – 0)	-	0.000*	0.000*	0.020*
K(+)	1 (1 – 3)	-	-	0.000*	0.000*
Di	0 (0 – 1)	-	-	-	0.103
Di+	0 (0 – 1)	-	-	-	-
p	0.000				
Group	**Steatosis median (min-max)**	**p¹**			
		K-	K+	Di	Di+
K(-)	0 (0 – 0)	-	0.000*	0.000*	0.020*
K(+)	1 (1 – 3)	-	-	0.000*	0.000*
Di	0 (0 – 1)	-	-	-	0.349
Di+	0 (0 – 1)	-	-	-	-
p	0.000				

(*) indicate significant differences (p < 0.05); NAFLD: non-alcoholic fatty liver disease; he healthy control group (K-) was provided with standard feed and water ad libitum.
The obesity control group (K+) was subjected to a high-fat, high-fructose diet (HFFD) for 28 days to induce obesity. The dadih group (Di) consisted of obese rats receiving 2 mL/200 g BW/day of dadih. The selenium-fortified dadih group (Di+) consisted of obese rats receiving 2 mL/200 g BW/day of selenium-fortified dragon fruit dadih.

the K+ group had significantly higher scores for inflammation, ballooning and steatosis compared to the K- group ($p < 0.05$), confirming that a high-fat, high-fructose diet induces liver damage. Both the Di and Di+ groups exhibited reductions in inflammation, ballooning and steatosis compared to the K+ group. However, the difference between Di and Di+ was not statistically significant ($p > 0.05$), suggesting that both interventions provided similar protective effects. However, the Di+ group tended to have lower scores than the Di group, indicating a potential additional benefit of selenium fortification in mitigating liver damage.

Discussion

The findings indicate that the HFFD model effectively induced obesity, as evidenced by significant increases in body weight and Lee index values. This condition was associated with elevated hepatic SREBP-1c expression in the obesity control group (K+), reflecting enhanced lipogenesis. In contrast, the groups receiving *dadih* (Di) and selenium-fortified dragon fruit *dadih* (Di+) exhibited a marked reduction in SREBP-1c levels, with the most significant decrease observed in the Di+ group. These results suggest that both interventions, particularly the selenium-fortified formulation, may suppress hepatic lipogenesis in the context of diet-induced obesity. Obesity disrupts the balance between lipid production, storage and oxidation, thereby promoting lipid accumulation in non-adipose tissues such as the liver and contributing to metabolic dysfunction.[8-10]

The administration of HFFD in the K+, Di and Di+ groups led to a significant increase in SREBP-1c expression compared to the K- group. The higher activation of SREBP-1c in the K+ group indicates that a high-fat, high-fructose diet enhances lipogenesis in hepatocytes, which is associated with excessive triglyceride synthesis and a decrease in fatty acid oxidation in the liver.[1, 11] Administration of *dadih* (Di) and selenium-fortified *dadih* (Di+) resulted in lower SREBP-1c expression compared to the K+ group, with a greater reduction observed in the Di+ group. This effect may be attributed to the role of probiotics in *dadih*, which contribute to gut microbiota balance and reduce systemic inflammation.[12, 13]

Several mechanisms explain the role of probiotics in the development of obesity and their relationship with SREBP-1c. One of these mechanisms involves fasting-induced adipocyte factor (FIAF), which functions as an inhibitor of lipoprotein lipase (LPL) and prevents fatty acid uptake by adipose tissue and the liver. Increased FIAF levels can suppress lipid accumulation in hepatocytes, thereby indirectly reducing SREBP-1c expression and inhibiting the progression of steatosis. Additionally, FIAF plays a role in enhancing fatty acid oxidation in the liver and muscles, which helps alleviate metabolic stress and suppress the inflammatory response triggered by excessive lipid accumulation.[14]

Furthermore, the decreased expression of SREBP-1c in the Di+ group compared to *dadih* without fortification (Di) indicates the superior effect of dragon fruit and selenium in fortified *dadih*. This suggests their role in inhibiting SREBP-1c activation, which supports enhanced fatty acid

oxidation and reduces triglyceride accumulation in the liver.[15] The addition of dragon fruit can enrich the prebiotic content of *dadih* and support the growth and activity of beneficial gut microbiota. Meanwhile, selenium in fortified *dadih* acts as an antioxidant by serving as a crucial component of glutathione peroxidase, an enzyme with antioxidant properties that breaks down lipid hydroperoxides. This process helps reduce lipid peroxidation and contributes to the regulation of lipid metabolism.[16, 17]

Liver histopathology also revealed significant differences among the treatment groups. Although the 28-day obesity induction period was relatively short to produce a clear steatosis pattern in the rat liver, structural changes in hepatocytes were already evident, with signs of inflammation and hepatocyte ballooning. This relatively short intervention period was chosen based on pilot observations and previous studies, which have shown early hepatic alterations within four weeks of high-fat diet feeding.[18] However, standard models of NAFLD often require at least 8 weeks to induce more advanced liver damage. Despite this limitation, the observed histopathological changes in the present study still provide valuable insights into the early hepatic response to dietary modulation. The K+ group exhibited increased inflammation and hepatocyte morphological alterations, which could lead to the development of steatosis. These findings help bridge the gap between the early signs of hepatic stress and the eventual onset of NAFLD. This suggests that, even before reaching the steatosis stage, obesity leads to endoplasmic reticulum (ER) stress in hepatocytes, initiating the unfolded protein response (UPR), which in turn can stimulate SREBP-1c activation. Under ER stress conditions, SREBP-1c activation promotes increased synthesis of fatty acids and triglycerides in the liver, contributing to hepatic lipid accumulation, which initially manifests through inflammation.[19, 20] This finding supports previous research which demonstrated that lipid accumulation in hepatocytes can trigger an inflammatory response that contributes to the progression of NAFLD.[21]

Conversely, the Di and Di+ groups exhibited improvements in liver histopathology, with reduced inflammation scores, although structural changes in hepatocytes were still observed. The Di+ group showed better outcomes than the Di group, indicating that the addition of dragon fruit and selenium in fortified *dadih* provided additional protective effects against obesity-induced liver damage. Selenium is known to have potent antioxidant activity through the activation of glutathione peroxidase (GPx), which plays a role in reducing oxidative stress and inflammation in the liver.[22] Selenium supplementation has also been found to suppress fat accumulation by modulating the peroxisome proliferator-activated receptor gamma (PPARγ) pathway, a process facilitated by antioxidant selenoenzymes. A previous study demonstrated that selenium supplementation can mitigate lipid-related metabolic disorders, such as hypertriglyceridemia and fatty liver disease.[15] Additionally, the flavonoid content in dragon fruit contributes to reducing inflammation and improving liver function.[23]

The findings of this study suggest that selenium- and dragon fruit-fortified *dadih* intervention could be a potential strategy for mitigating the adverse effects of obesity on lipid metabolism and liver health. Further studies are needed to explore the underlying molecular mechanisms of this protective effect, particularly regarding the regulation of lipogenic genes and the role of gut microbiota in lipid metabolism. Thus, the combination of probiotics from *dadih*, antioxidants from dragon fruit and selenium may synergistically prevent the progression of NAFLD and metabolic complications associated with obesity.

Study limitations

This study has several limitations that should be acknowledged. First, the duration of obesity induction and dietary intervention was limited to 28 days, which may not be sufficient to fully replicate the pathological progression of NAFLD, particularly the development of advanced steatosis or fibrosis. Although early histopathological changes, such as hepatocyte ballooning and inflammation, were evident, standard NAFLD models often require at least 8 weeks to induce more advanced hepatic damage. Nonetheless, future studies with longer intervention durations are necessary to evaluate the sustained efficacy and safety of selenium-fortified dragon fruit *dadih*.

Second, the study did not include key biochemical markers, such as serum triglycerides, total cholesterol, liver enzymes (AST and ALT) and fasting blood glucose. These parameters are

essential for assessing systemic metabolic status and would have provided a more comprehensive picture of the intervention's effects. Although histopathological and gene expression data offer valuable insights, the absence of biochemical profiles limits the metabolic interpretation of the findings. Future studies should integrate these biochemical assessments to strengthen the clinical relevance of the results.

Third, the molecular analysis in this study was limited to SREBP-1c expression. While this transcription factor is a central regulator of lipogenesis, the inclusion of additional genes involved in lipid metabolism, oxidative stress and inflammatory signalling (eg, PPARγ, FASN, ACC, GPx) would have enriched the mechanistic understanding of the observed effects. Further investigations involving broader molecular profiling are needed to elucidate the pathways by which selenium-fortified dragon fruit *dadih* modulates hepatic metabolism under obese conditions.

Taken together, while the present study demonstrates promising results regarding the potential hepatoprotective effects of selenium-fortified dragon fruit *dadih*, future research with longer durations, expanded biochemical and molecular analyses and translational models is warranted to validate and extend these findings.

Conclusion

The findings of this study indicate that consuming selenium-fortified dragon fruit *dadih* significantly lowered SREBP-1c expression in rats with obesity induced by a high-fat, high-fructose diet. The control group receiving the obesogenic diet exhibited increased SREBP-1c expression, accompanied by early histopathological changes such as hepatocyte ballooning and inflammation, suggesting the onset of hepatic dysfunction. Although advanced steatosis was not observed, likely due to the relatively short intervention duration, the findings reflect an early progression towards fatty liver disease.

The intervention with dragon fruit *dadih* showed protective effects against excessive lipogenesis, which were further enhanced by selenium fortification. These results highlight the potential of selenium-fortified dragon fruit *dadih* as a functional food candidate for preventing metabolic disturbances associated with obesity. However, considering the study's limitations—including the short duration of the intervention, the absence of biochemical markers and the restricted scope of molecular analyses—further studies are needed. Future research should employ longer intervention periods, incorporate comprehensive biochemical and molecular assessments and explore translational models to validate and deepen the understanding of the protective mechanisms provided by selenium-fortified dragon fruit *dadih*.

Ethics

This study was conducted in accordance with the ethical guidelines for animal research and was approved by Institutional Animal Ethics Committee of Universitas Diponegoro, approval No: 090/EC-H/KEPK/FK-UNDIP/IX/2024, dated 4 September 2024.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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References

1. Moon YA. The SCAP/SREBP Pathway: A mediator of hepatic steatosis. Endocrinol Metab. 2017;32(1):6. doi: 10.3803/EnM.2017.32.1.6.
2. Usmiati S, Risfaheri. [Development of Dadih as a functional probiotic food native to West Sumatra]. J Litbang Pert. 2015;32(1):20-9. doi: 10.21082/jp3.v32n1.2013. Indonesian.
3. Lu S. The role of lactic acid bacteria in gut microbiota and mucosal immune system. E3S Web Conf. 2021;271:03075. doi: 10.1051/e3sconf/202127103075.
4. Suharti. [Hedonic test and hedonic quality of buffalo milk curd with the addition of different fruit extracts]. Univ Islam Negeri Sultan Syarif Kasim Riau. http://repository.uin-suska.ac.id/id/eprint/40288. Indonesian.
5. Maleta HS, Kusnadi J. [The effect of adding red dragon fruit (Hylocereus Polyrhizus) juice on the antioxidant activity and physicochemical characteristics of Caspian Sea yogurt]. J Pangan dan Agroindustri. 2018;6(2):13-22. doi: 10.21776/ub.jpa.2018.006.02.2. Indonesian.
6. Nido SA, Shituleni SA, Mengistu BM, Liu Y, Khan AZ, Gan F, et al. Effects of selenium-enriched probiotics on lipid metabolism, antioxidative status, histopathological lesions, and related gene expression in mice fed a high-fat diet. Biol Trace Elem Res. 2016 Jun;171(2):399-409. doi: 10.1007/s12011-015-0552-8.
7. Mohran MA, Tammam AA. Chemical, microbiological, rheological and sensory properties of yoghurt fortified with selenium. Assiut J Agric Sci. 2020;50(4):51-63. doi: 10.21608/ajas.2020.70972.
8. Lasker S, Rahman MM, Parvez F, Zamila M, Miah P, Nahar K, et al. High-fat diet-induced metabolic syndrome and oxidative stress in obese rats are ameliorated by yogurt supplementation. Sci Rep. 2019 Dec 27;9(1):20026. doi: 10.1038/s41598-019-56538-0.
9. Ferré P, Foufelle F. Hepatic steatosis: a role for de novo lipogenesis and the transcription factor SREBP-1c. Diabetes Obes Metab. 2010;12(s2):83-92. doi: 10.1111/j.1463-1326.2010.01275.x.
10. Rosas-Villegas A, Sánchez-Tapia M, Avila-Nava A, Ramírez V, Tovar A, Torres N. Differential effect of sucrose and fructose in combination with a high fat diet on intestinal microbiota and kidney oxidative stress. Nutrients. 2017;9(4):393. doi: 10.3390/nu9040393.
11. Ponugoti B, Kim DH, Xiao Z, Smith Z, Miao J, Zang M, et al. SIRT1 deacetylates and inhibits SREBP-1C activity in regulation of hepatic lipid metabolism. J Biol Chem. 2010 Oct 29;285(44):33959-70. doi: 10.1074/jbc.M110.122978.
12. Jurnalis YD. [The effect of curd administration on intestinal microflora balance and ileal villi height]. Sari Pediatr. 2020;21(4):207. doi: 10.14238/sp21.4.2019.207-12. Indonesian.
13. Supiyani A, Agussetiandari I, Handayani T, Sukmawati D. [Effect of synbiotic milk on duodenal mucosal structure of mice induced by high dose trans trans oil: an experimental animal study]. Heal Inf J Penelit. 2023;15(1):23-31. doi: 10.36990/hijp.v15i1.673. Indonesian.
14. Sun L, Ma L, Ma Y, Zhang F, Zhao C, Nie Y. Insights into the role of gut microbiota in obesity: pathogenesis, mechanisms, and therapeutic perspectives. Protein Cell. 2018;9(5):397-403. doi: 10.1007/s13238-018-0546-3.
15. Zhang Q, Zhou X, Zhang J, Li Q, Qian Z. Selenium and vitamin B6 cosupplementation improves dyslipidemia and fatty liver syndrome by SIRT1/SREBP-1c pathway in hyperlipidemic Sprague-Dawley rats induced by high-fat diet. Nutr Res. 2022;106(6):101-18. doi: 10.1016/j.nutres.2022.06.010.
16. Oztürk Z, Gurpinar T, Vural K, Boyacıoglu S, Korkmaz M, Var A. Effects of selenium on endothelial dysfunction and metabolic profile in low dose streptozotocin induced diabetic rats fed a high fat diet. Biotech Histochem. 2015;90(7):506-15. doi: 10.3109/10520295.2015.1042050.
17. Fairweather-Tait SJ, Bao Y, Broadley MR, Collings R, Ford D, Hesketh JE, et al. Selenium in human health and disease. Antioxid Redox Signal. 2011 Apr 1;14(7):1337-83. doi: 10.1089/ars.2010.3275.
18. Hidayati L, Widodo ADW, Hidayat B. Animal models with metabolic syndrome markers induced by high fat diet and fructose. Med Lab Technol J. 2020;6(1). doi: 10.31964/mltj.v6i1.266.

19. Kammoun HL, Chabanon H, Hainault I, Luquet S, Magnan C, Koike T, et al. GRP78 expression inhibits insulin and ER stress-induced SREBP-1c activation and reduces hepatic steatosis in mice. J Clin Invest. 2009 May;119(5):1201-15. doi: 10.1172/JCI37007.
20. Imanuel Setiawan S, Kurniawan J. [Treatment options for non-alcoholic fatty liver disease (NAFLD)]. Cermin Dunia Kedokt. 2021;48(3):173. doi: 10.55175/cdk.v48i3.1336. Indonesian.
21. Kim JY, Garcia-Carbonell R, Yamachika S, Zhao P, Dhar D, Loomba R, et al. ER stress drives lipogenesis and steatohepatitis via caspase-2 activation of S1P. Cell. 2018 Sep 20;175(1):133-45.e15. doi: 10.1016/j.cell.2018.08.020.
22. Zhao D, Gao F, Zhu H, Qian Z, Mao W Yin Y, et al. Selenium-enriched bifidobacterium longum DD98 relieves metabolic alterations and liver injuries associated with obesity in high-fat diet-fed mice. J Funct Foods. 2020;72(June):104051. doi: 10.1016/j.jff.2020.104051.
23. Febriani W, Komala R, Yunianto AE. [The potential of red dragon fruit as an anti-diabetes and health maintenance agent: a review]. Media Ilm Kesehat Indones. 2024;2(3):111-9. doi: 10.58184/miki.v2i3.349. Indonesian.